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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/257,585	02/25/1999	SALLY A. LEONG	P98067US	2444

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DANN DORFMAN HERRELL & SKILLMAN
SUITE 720
1601 MARKET STREET
PHILADELPHIA, PA 19103-2307

EXAMINER
KUBELIK, ANNE R

ART UNIT	PAPER NUMBER
1638	17

DATE MAILED: 04/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/257,585	Applicant(s) LEONG ET AL.	
	Examiner Anne Kubelik	Art Unit 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-17,25 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-17,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5)☐ Notice of Informal Patent Application (PTO-152)

3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6)☐ Other

DETAILED ACTION

1. The request filed on 22 January, 2002, for a Request for Continued Examination (RCE) under 37 CFR 1.114 of Application No. 09/257,585 is acceptable and an RCE has been established. An action on the RCE follows.

2. The amendments to claims 1-3, 5-9, 11, 13-16 and 25-26 requested in Paper No. 16, filed 22 January, 2002, have been entered. Claims 1-11, 13-17 and 25-26 are pending.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

4. The rejections of claims 11-17 under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is WITHDRAWN in light of Applicant's pointing to specific support for the amendments.

Claim Objections

5. Claims 2-3 and 11 are objected to because of the following informalities:

"nucleotide" in claims 2, lines 4 and 5, claim 3, lines 3 and 4 and claim 11, lines 6 and 7, should be plural.

Claim Rejections - 35 USC § 112

6. Claims 1-11, 13-17 and 25-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid of SEQ ID NO:1 and bacterial and fungal cells transformed with that nucleic acid, does not reasonably provide enablement for nucleic acids that encode "allelic variants" of SEQ ID NO:1 or its open reading frames or that hybridize to those nucleic acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to a multitude of nucleic acids that encode "allelic variants" of SEQ ID NO:1 or its open reading frames or that hybridize to those nucleic acids, and cells transformed with those nucleic acids.

The instant specification, however, only provides guidance for map-based cloning of the AVR1-CO39 gene from *Magnaporthe grisea* strain 2539 and identification of 1.05 kb region (SEQ ID NO:1) that transforms a virulent *M. grisea* isolate to an avirulent one (pg 23-24), identification of 6 open reading frames (ORFs) within SEQ ID NO:1 (SEQ ID NOs:2-7; pg 27-29), creation of frameshift mutations in ORF1, ORF2 and ORFs 2 and 3 and substitution mutations of the ATG start codon of ORFs 1-3 and the testing of those mutants for loss of avirulence (pg 25-26 and 29), hybridization experiments using SEQ ID NO:1 as a probe against genomic DNAs of various *M. grisea* isolates (pg 30), and improved resistance of rice plants sprayed with the ORF3 protein or with *Escherichia coli* transformed with a nucleic acid encoding ORF 3 (pg 30-31).

must not be changed, to maintain avirulence activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional protein. The instant specification fails to provide guidance for plant cells transformed with SEQ ID NO:1 or its open reading frames.

The specification on pg 29 shows that mutations in ORFs 1 and 3 (but not ORF2) eliminated their avirulence function and that the protein encoded by ORF3 provided plants with resistance to *M. grisea*. However, in a journal article published January, 2002, (Farman et al, 2002, Mol. Plant. Microbe Interact. 15:6-16) Applicant stated that while subcloning and transformation experiments had localized the AVR1-CO39 avirulence function to a 1.05kb region of DNA, the exact location of that function had still - almost 4 years after the filing date of the instant application - not been defined (pg 6, right column, paragraph 1). Thus, the identification of any portion of SEQ ID NO:1 as conferring CO-39-specific avirulence is questionable, and the specification does not teach how to use nucleic acids encoding SEQ ID NOs:2-3, or 5-7.

Farman et al (*supra*) also teach that 39 *M. grisea* isolates completely lacked any version of the AVR-CO39 gene (Table 1). Five Japanese *M. grisea* isolates, when probed with the 1.05 kb fragment showed a strong hybridization signal, but all the isolates were highly virulent on rice cultivar CO-39. Farman et al conclude, "Therefore, the AVR-CO39 homologs present in these isolates do not function as avirulence genes" (paragraph spanning pg 8-11). Thus, it is not apparent that any *M. grisea* strain other than the one from which SEQ ID NO:1 was isolated has a nucleic acid that confers CO-39-specific avirulence.

Mutations that resulted in single amino acid substitutions in avirulence proteins from

[illegible]

[illegible] see pg [illegible] right column

paragraph 3; Rohe et al, 1995, EMBO J. 14:4168-4177, see pg 4172, paragraph spanning the columns; Jia et al, 2000, EMBO J. 19:4004-4014, see pg 4011, left column, paragraph 2). Many of these mutations replaced cysteine with another amino acid or mutated critical active site amino acids in the encoded protein.

However, the protein of SEQ ID NO:4 has only 3 cysteine (out of 90 amino acids) and Applicant has not identified any critical structural features or amino acids. Given the claim breath, unpredictability, and lack of guidance provided in the specification, undue experimentation would have been required by one skilled in the art to develop and evaluate "allelic variants" or nucleic acids that would hybridize to SEQ ID NO:1 or its open reading frames. Making all possible amino acid substitutions in all the amino acids of SEQ ID NO:4 other than the cysteines and the starting methionine would require making and analyzing 4^{86} nucleic acids. All of these nucleic acids would have greater than 99% identity to a nucleic acid that encodes SEQ ID NO:4.

Lastly, expression of fungal avirulence genes in plants can be lethal. Gopalan et al (1996, Plant Cell 8:1095-1105) teach that transformation of the *AvrB* gene into *RPM1* resistance gene-containing *Arabidopsis* cells and plants is lethal (pg 1098, right column, to pg 1099). Applicant provided no working examples in which the AVR-CO39 gene was transformed into plant cells to show that this unpredictability has been overcome.

Therefore, the claims are not enabled for nucleic acids that encode "allelic variants" of SEQ ID NO:1 or its open reading frames or that hybridize to those nucleic acids, and cells transformed with those nucleic acids.

Applicant's arguments filed 22 January, 2002 have been fully considered but they are not

SEQ ID NO:1 to confer CO-39 cultivar specificity and the roles of ORFs 1 and 3 in avirulence are taught in example 1. Applicant urges that the significant experimentation required to initially identify SEQ ID NO:1 is the reason why SEQ ID NO:1 is novel but is not relevant to whether the specification is enabling to the invention as claimed.

This is not found persuasive because the claims are drawn to nucleic acids that hybridize with SEQ ID NO:1 and Forman et al teach that several isolates whose DNA hybridizes to SEQ ID NO:1 do not have avirulence on CO39, as discussed above. Applicant fails to teach the sequences that distinguish AVR-CO39 homologs that confer avirulence from those that do not.

7. Claims 1-11, 13-17 and 25-26 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is repeated for the reasons of record as set forth in the Office actions mailed 30 May, 2001, and 7 September, 2000.

Applicant's arguments filed 22 January, 2002 have been fully considered but they are not persuasive. Applicant urges that the claim recites an isolated nucleic acid with specific structural features (it is 1 kb long, has at least one open reading frame and hybridizes under specified conditions to SEQ ID NO:1) and functional features (it is a *M. grisea* nucleic acid that confers CO-39 specific avirulence to fungal plant pathogens). Applicant also urges that although the specification only describes the sequence of one member of the genus it nonetheless described more than one member of the genus because hybridization experiments showed that homologs of SEQ ID NO:1 exist in *Setaria*-infecting *M. grisea* isolates.

structural feature is not described - virtually any piece of DNA encodes an open reading of at least a couple of amino acids; thus, the presence of an open reading frame of unspecified sequence does not provide a specific description of a nucleic acid. Additionally, the specification does not describe the structural features that distinguish AVR-CO39 homologs that confer avirulence from those that do not.

Lastly, the recited hybridization conditions are of such low stringency, especially as hybridization and wash times are not recited, that the claims can be said to encompass about 4^{1000} nucleic acids. Applicant has only described one of those.

See *In re Shokal,* 113 USPQ 283, (CCPA 1957) at pg 285

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189 ; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary. ...
> We are of the opinion that a genus containing such a large number of species cannot properly be identified by the mere recitation or reduction to practice of four or five of them. As was pointed out by the examiner, four species might be held to support a genus, if such genus is disclosed in clear language; but where those species must be relied on not only to illustrate the genus but to define what it is, the situation is otherwise.

8. Claims 1-3, 5, 8-9, 11, 15-16 and 25-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention.

Claims 1, 11 and 25 are indefinite in their recitation of hybridization conditions. Because hybridization and wash times are not recited, the meets and bounds of the claims are unclear.

Claims 2-3 and 11 are not written in proper Markush format. The claims should be in the format "selected from the group consisting of A, B, C and D." The "and" is missing at the end of

"having" in claim 5 should be replaced with --of--.

Claims 6 and 13 are unclear - does the recombinant DNA comprise the vector or does the vector comprise the recombinant DNA?

Claims 11 and 26 are indefinite in their recitation of "allelic variant". The extent to which the nucleic acid varies from SEQ ID NO:1 is unclear, especially since Forman et al (*supra*) teach that many avr1-CO39 alleles are null alleles (pg 13) and since the specification does not define the term.

Claims 8-9 and 15-16 lack antecedent basis for the limitation "The cell" in line 1. The claims upon which they depend are drawn to "fungal, bacterial or plant" cells.

Claim Rejections - 35 USC § 102

9. Claims 11 and 13-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Sweigard et al (1995, Plant Cell 7:1221-1233).

Sweigard et al teach a *M. grisea* gene (Figure 6) that would be an "allelic variant" of SEQ ID NO:1 or an open reading frame of SEQ ID NO:2 or would hybridize to such an allelic variant under the conditions listed in claim 11, part (e). This gene is in a vector and transformed into the fungus *M. grisea* and the epiphytic bacteria *E. coli* (pg 1233, paragraph spanning the columns, and pg 1230, left column).

10. Claims 11 and 13-16 remain rejected under 35 U.S.C. 102(b) as being anticipated by Shimizu et al (1991, Infect. Immunol. 59:137-142). The rejection is repeated for the reasons of record as set forth in the Office actions mailed 30 May, 2001, and 7 September, 2000.

Applicant's [illegible] have been amended to recite the invention

conditions, which are sufficiently stringent that only hybrids with a homology of greater than 95% would be detected. This is not found persuasive because the hybridization and wash times are not recited. Thus, the recited hybridization conditions would detect nucleic acids with a homology of much less than 95%.

11. Claims 1-10, 17 and 25-26 are free of the prior art, given the failure of the prior art to teach or suggest an isolated nucleic acid of SEQ ID NO:1 or *M. grisea* nucleic acids from chromosome 1 that hybridize to SEQ ID NO:1 or its open reading frames and cells transformed with those nucleic acids, and given the unpredictability discussed above.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kimberly Davis, at (703) 305-3015.

Anne R. Kubelik, Ph.D.
April 5, 2002

AMY J. NELSON, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600